REMARKS

STATUS OF THE CLAIMS

Claims 83-87 were pending in this application. Claims 83-87 have been amended. Following entry of the amendments Claims 83-87 will be pending and at issue.

SUPPORT FOR AMENDMENTS TO THE CLAIMS

Claims 83, 85, 86 and 87 have been amended to substitute the term "modulate expression of a selected nucleic acid" for the term "possess at least one property." This amendment more clearly defines Applicants' invention and makes clear that Claims 83 (and its dependent, Claim 84), 85, 86 and 87 relate to "system[s] of associated components for preparing a set of oligonucleotides that modulates expression of a selected nucleic acid." These claims also have been amended to substitute the term "system" for the term "network" to more clearly define Applicants' invention.

Claim 84 has been amended to remove the abbreviation "UTR" and substitute in its place the term "untranslated region."

The amendments to the claims are supported throughout the specification as filed at, e.g., the places indicated in the table below, and therefore add no new matter.

Amended term	**Claim(s)**	**Exemplary support**
modulates expression of a selected nucleic acid	83, 85, 86, 87	p. 2, lines 21-26; p. 56, line 30 - p. 58, line 5
system	83, 85, 86, 87	p. 2, 23-26, p. 3, lines 21-27; p. 7, lines 25-28; p. 9, lines 33-35; Figure 18
untranslated region	84	p. 25, lines 9-12; Figure 9

IDS

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the IDS (Form 1449) submitted on May 15, 2003.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 84 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for containing abbreviations without the full name indicated in the claim. Applicants have amended the claim to delete reference to the "UTR" abbreviation and substitute in its place the full name "untranslated region." Withdrawal of this basis for rejection is requested.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 83 and 85-87 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Agrafiotis et al. (P/N 5,463,564) taken in view of Hyndman et al. [Biotechniques 20(6):1090(1996)] and Nickerson et al. [PNAS 87:8923(1990)] Applicants traverse this ground of rejection by amendment and argument.

Three requirements must be met for a prima facie case of obviousness. First, the prior art references must teach all the limitations of the claims. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. Third, a reasonable expectation of success is required.

The instantly claimed invention is directed to systems of associated components for preparing a set of oligonucleotides that modulate expression of a selected nucleic acid. The system addresses and solves problems in the art relating to, e.g., the unpredictability associated with identifying active oligonucleotide compounds, and the failure of traditional structure activity relationship (SAR) studies to deal with the fact that "RNA structure can inhibit duplex formation with antisense compounds, so much so that "moving" the target nucleotide sequence even a few bases can drastically decrease the activity of such compounds (Lima *et al., Biochemistry*, 1992, 31, 12055)." Specification at p. 3, lines 3-8; *see also* p. 3, lines 9-27 for additional description of problem addressed by instantly claimed invention.

The cited prior art references do not teach all of the elements of the claims. Specifically, none of the references, alone or in combination teaches a system of associated components for preparing a set of oligonucleotides that modulate expression of a selected nucleic acid. The system includes components to prepare a virtual library of oligonucleotides targeted to a selected nucleic acid, reduce the members of the virtual library by a process of selection based on one or more of the following: 1) targeting a functional region of the selected nucleic acid (Claims 83 – 87); 2) target accessibility (Claims 85 – 87); 3) uniform distribution of oligonucleotide compounds across the selected nucleic acid (Claims 85 – 87). Each of these methods uses sequence information about the target to prepare the virtual library.

Agrafiotis is cited for its teaching of an automated system with components for virtual compound design, synthesis, and testing. *See* Office Action at p. 2. The Examiner suggests that this teaching motivates, summarizes and suggests virtual compound design and selection. References must be read as a whole, including parts that would tend to teach away from Applicants' claimed invention. Applicants respectfully submit that Agrafiotis is directed to a problem different from that solved by Applicants' claimed invention, *i.e.,* that of constraining chemical diversity space through the use of a "directed diversity" chemical library, compound testing, and iterated optimization based on the test results. *See, e.g.,* Agrafiotis at col. 5, lines 1-30, and col. 8, lines 31-37. In the oligonucleotide context, Agrafiotis generically suggests their use as "random bio-oligomers" (*see* Agrafiotis at col. 9, lines 6-11) for generating chemical diversity libraries using alternative chemistries. Thus, Agrafiotis' approach using "random" bio-oligomers to discover active compounds teaches away from Applicants' use of target sequence information to reduce members of the virtual library.

Hyndman is cited for its teachings that "summarize[] the desirability of oligonucleotides as essential components for a variety of biological procedures, inclusive of nucleic acid detection or antisense inhibition of gene expression..." *See* Office Action at p. 4. Hyndman teaches a computer program (HYB*simulator*) that uses input criteria such as melt temperature, free energy and length to design a probe set against a target sequence, but then identifies preferred probes by

eliminating sequences with insufficient target specificity. *See* Hyndman at p. 1092, carry over paragraph describing selecting most favorable sub-sequences, at p. 1092 right column first full paragraph, and Figure 4 describing a process for displaying differences in probe specificity, or retaining probes expected to hybridize to all targets of interest (Hyndman at p. 1094, first full paragraph), or retaining probes expected to perform well in PCR amplifications (*see id.* under "Basic PCR" heading). Hyndman's use of Hyb*simulator* to design potential antisense compounds also illustrates that specificity, (not target functional region), is the basis for selecting sequences to test. *See* Hyndman Fig. 5.

Accordingly, the combination of Agrafiotis with Hyndman does not teach or suggest the elements of a system that "reduces the members of the virtual library by a process of selection based on" one or more of the following: 1) "targeting a functional region of said selected nucleic acid" (Claims 83 – 87); 2) "target accessibility" (Claims 85 – 87); 3) "uniform distribution of oligonucleotide compounds across the selected nucleic acid" (Claims 85 – 87). The combination cannot render the claims obvious.

Furthermore, the combination of Agrafiotis with Hyndman fails to teach or suggest the limitation of "an apparatus that accepts said set of real oligonucleotides and performs at least one procedure for each of said real oligonucleotides wherein said procedure identifies particular members of said set that modulate the expression of said selected nucleic acid, wherein said procedure is computer-controlled polymerase chain reaction or computer-controlled enzyme-linked immunosorbent assay" (Claims 83, 85, 86, and 87) or "a second apparatus selected from the group consisting of liquid chromatography, optical density reader, mass spectroscopy, gel fluorescence and scintillation imaging, and capillary gel electrophoresis" (Claim 85).

Nickerson et al. does not remedy these deficiencies, as it teaches an automated analytical method (PCR + ELISA) for detecting the presence of a known DNA sequence in a sample. (*See* Office Action at p. 5, first full paragraph, and carry over paragraph on p. 6.) Thus, it does not teach or suggest Applicants' elements of reducing the members of the virtual library of oligonucleotides according to target accessibility, uniform distribution of oligonucleotide

compounds, or targeting a functional region of the selected nucleic acid. Neither does Nickerson et al. teach or suggest Applicants' combination of reducing members (as claimed) with an apparatus that accepts the real oligonucleotides and performs a computer -controlled test to determine whether a real oligonucleotide modulates target expression using computer-controlled polymerase chain reaction or computer-controlled enzyme-linked immunosorbent assay. Nickerson et al.'s teaching in combination with Agrafiotis and Hyndman at best suggests automated methods for designing and testing PCR probes and using them in combination with ELISA to first amplify and then detect the presence of a suspected nucleic acid sequence (i.e., diagnostic applications), not Applicants' claimed invention directed to a system of associated components for preparing a set of oligonucleotides that modulate expression of a selected nucleic acid.

Similarly, neither do the cited sections of Cutting et al. (describing target mutation site at a stop codon; *see* Office Action at p. 7, second full paragraph), or the cited sections of Albertsen et al. (describing PCR primers directed to start or initiator codon deletion mutations; *see* Office Action at p. 7, third full paragraph) remedy the deficiencies of the primary references to teach or suggest the Applicants' claimed combination, as there is nothing in either the Cutting et al. or the Albertsen et al. reference (teaching various mutations in gene regions) to teach or suggest reducing a virtual set of oligonucleotides by targeting regions such as the stop codon or start codon, or an apparatus that accepts real oligonucleotides and performs a procedure (computer-controlled polymerase chain reaction or computer-controlled enzyme-linked immunosorbent assay) to identify set members that modulate expression of the selected nucleic acid.

In conclusion, a prima facie case of obviousness is not made. Withdrawal of this ground of rejection of Claims 83-87 is respectfully requested.

PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 83 and 85-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55, 56, 58-72, 74-87, and 99-102 of copending Application No. 09/295,463. Applicants state that the conflicting

application is commonly owned with the instant application and Applicants will execute a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) once the conflicting claims have been patented.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicants' representative at (415) 875-2413.

Respectfully submitted,
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